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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SEHARASEYON, JEGATHEESAN	
ART UNIT	**PAPER NUMBER**
1647	15

DATE MAILED: 12/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/813,329	CARROLL ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This office action is in response to the amendment and remarks filed on 8/6/03 in Paper No: 17. Applicant has amended claims 1, 2 and 7. Claims 1-12 are pending.

2. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

3. Any objection or rejection of record, which is not expressly repeated in this action, has been overcome by Applicant's response and withdrawn.

4. The Office acknowledges the receipt of substitute specification that was submitted 6/25/2001 and the amendments to the substitute specification submitted on 10/30/02. These have been entered into the record.

5. The corrected drawings submitted on 6/30/03 have been received by the Office and entered.

6. The Office acknowledges the change in the title.

7. The Office acknowledges the error in the previous Office action where the instant protein was inadvertently referred to as a transport protein.

8. The Office does not require the Applicant to provide the program information or the parameters when reciting claims with % identity.

Claim Rejections - 35 USC § 101, maintained

9. Claims 41-66 stand rejected under 35 USC 101 for lack of utility, for reasons set forth in Paper No: 11. Applicant's arguments filed on 8/06/03 in reference to claims 41-63 have been fully considered but they are not persuasive.

Applicant has traversed this rejection on the premise that the disclosure of the probable fact that a protein of the instant invention functions as a tumor necrosis factor (DmTNFv2) protein is sufficient utility. Applicant asserts that the present invention, which is drawn to isolated nucleic acid molecules (SEQ ID No: 5) that encode a tumor necrosis factor protein (SEQ ID No: 6), involved in "modulating the innate immune response in invertebrates, particularly flies, and most preferably in Drosophila" (response page 12 and specification page 53, lines 30-35). Applicant further asserts that inherent in the asserted utility for modulating innate immune responses in Drosphila is the utility of DmTNFv2 in modulating cell death and proliferation, including apoptosis (see response page 12 and specification page 80-81) and the Jun N-terminal protein kinases (JNK) pathway (see page 2). Applicant's arguments have been fully considered but are not deemed persuasive.

Applicants assert that these utilities are "specific" since they are specific to immune disorders afflicting flies, and not any disorder. Applicants further assert that these utilities are 'substantial" since disorders afflicting innate immunity represents a significant source of mortality in Drosophila, for example, as well as in humans in the world today. However, the specification fails to identify immune disorders that are affected by DmTNFv2 protein. Applicant has not established a nexus between DmTNFv2 proteins and immune diseases.

Applicant further asserts that the specification teaches that DmTNFv2 shares significant identity to other TNF family members, such as the human osteoprotegerin protein, the human hCD27 ligand protein, the human CD30 ligand protein, the human

TRAIL protein, and the human ectodysplasmin_A protein. In addition, they also point to the putative TNF domain in the specification. These arguments are not persuasive for the following reasons. (1) Amino acid sequence identity to other TNF proteins is not sufficient for establishing utility because structural analogy to a known compound with a known activity and utility is not sufficient evidence of utility for the claimed compound (see *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966)). (2) Conservation of an TNF family domain does not provide a specific, substantial and credible utility for the claimed compound because not all of the TNF proteins of the family have the same utility. In other words, conservation of structure does not result in sufficient conservation of function to support having the same utility. This conclusion was supported by the Scott et al. reference in the previous Office action.

Applicants also argue about the development specific expression of DmTNFv2 in Drosophila embryos and its relationship to Rel proteins. They also teach the low level overexpression of DmTNFv2 in transgenic flies leading to lethality. Although, these findings are of scientific importance, the instant specification has not disclosed any real world utility that results from these observations.

Applicant further argues that invertebrates have a TNF pathway and in conjunction with its significant homology to known TNF family members, the presence of the conserved TNF domain, the negative regulation of DmTNFv2 by Rel proteins, and the evidence that low levels of DmTNFv2 expression leads to lethality, that one skilled in the art would have appreciated that DmTNFv2 is a TNF family member. Thus, they assert a biological role is ascribed to DmTNFv2 based on the sequence homology to

TNF and this DmTNFv2 has a specific and substantial utility. As discussed previously, conservation of a TNF domain does not provide a specific, substantial and credible utility for the claimed compound because not all of the TNF proteins of the family have the same utility. In other words, conservation of structure does not result in conservation of function.

Furthermore, Applicants argues at pages 14-16 of the response that one skilled in the art of immunology and invertebrate genetics, upon reviewing the totality of the evidence taught by the specification, would logically arrive at the conclusion that DmTNFv2 is a TNF family member. The fact that the protein of the instant invention has homology to TNF is not in dispute. However, that single fact is not sufficient to convey utility. In addition, Applicant asserts that DmTNFv2 is useful for modulating the innate immune response in invertebrates specifically in Drosophila due to its significant homology to known TNF family members, the presence of the conserved TNF domain, the negative regulation of DmTNFv2 by Rel proteins and the lethality phenotype. It is unclear how one of skilled in the art would utilize the modulation of the innate immune response in invertebrates by DmTNFv2 for real world use.

Applicants also cite Igaki et al. (2002) and Moreno et al. (2002) references to indicate that DmTNFv2 is indeed an invertebrate tumor necrosis factor superfamily ligand that can trigger cell death. These post filing references teach that the TNF homolog of the instant invention can induce cell death and also discuss its involvement in the Drosophila JNK pathway. This is a post filing information and clearly Applicants were not in possession of this at the time the application was filed. However, the

specification of the instant application does not teach which genes are affected by DmTNFv2 polypeptide except Rel protein. Since significant further research would be required by the skilled artisan to identify the genes involved in cell death that are affected by the claimed polypeptides, this asserted utility is not substantial. In addition, while it is true that DmTNFv2 appears to affect apoptosis, there is a great diversity of tissues and cell types affected by this class of polypeptides.

In addition, Applicants argues at pages 17-19 of the response that one skilled in the art would appreciate that DmTNFv2 is a TNF family member based upon the teachings of the instant specification and post filing teachings of Igaki et al. and Moreno et al. Applicants also argue that examples 2, 3 and 4 demonstrate that DmTNFv2 is negatively regulated by Rel, which is a TNF intracellular signaling molecule. Additionally, Applicants argue that example 5, demonstrates that that low levels of overexpression of DmTNFv2 in transgenic flies leads to lethality. However, pages 26-27 of the specification clearly contemplate the instant protein to be related to human osteoprotegerin ligand protein. In addition, the specification teaches that the "observed expression in Drosophila embryos, suggests the DmTNF polynucleotides and polypeptides of the present invention have uses which include treating, ameliorating, and/or preventing diseases and disorders related to aberrant osteoprotegerin ligand function." The specification also asserts that the claimed invention could be used in a "method of augmenting the ability of dendritic cells to stimulate naïve t-cell proliferation, in regulating interaction between t cells and dendritic cells, modulating the regulation of the t cell-dependent immune response, in addition to, potentially enhancing bone-

resorption in humoral hypercalcemia of malignancy, in animals, preferably humans. DmTNF may also be useful in modulating immune responses, and/or ameliorating or preventing morphological aberrations in insects, preferably in flies, such as Drosophila" (page 27, lines 5-15). In addition, the specification also recites that DmTNF polypeptide was also determined to share significant homology with both the human and mouse ectodysplasmin_A protein. It also asserts that mutations within ectodysplasin-A in mice has been shown in result in a Tabby phenotype (i.e., no sweat glands). Ectodysplasin-A has been shown to function in epithelial morphogenesis and promotes cell-matrix adhesion (page 27, lines 20-25). The specification also describes that mutations in the human ectodysplasmin-A has been directly implicated in X-linked anhidrotic (hypohidrotic) ectodermal dysplasia (page 27, lines 25-27). Thus it is asserted that, DmTNF polynucleotides and polypeptides, including fragments and/or antagonsists thereof, may have uses which include modulating epithelial morphogenesis, cell-matrix adhesion, in flies, preferably Drosophila, and potentially in other organisms as well, preferably mammals, such as humans, mice, and rats. Moreover it is asserted in the specification that, DmTNF polypeptides and polypeptides, including fragments and/or antagonists thereof, may have uses which include treating, ameliorating, and/or preventing X-linked anhidrotic (hypohidrotic) ectodermal dysplasia, including X-linked anhidrotic (hypohidrotic) ectodermal dysplasia-like disorders, such as sparse hair, abnormal or missing teeth, and sweat gland aberrations, in animals, preferably insects, and potentially in humans (page 27, lines 30-36). Neither the specification nor the prior art demonstrates a causal correlation or nexus of the claimed polypeptide with any of

the conditions or disorders contemplated by the instant specification, therefore, one skilled in the art would not consider the assertion that the specification would provide for a method of treating/diagnosing any of the listed conditions or disorders to be substantial.

In addition, one of ordinary skill in the art would not believe the assertions to be credible for treatment of the above listed conditions in light of the evidence in the specification that the claimed DmTNFv2 protein is negatively regulated by Rel, which is a TNF intracellular signaling molecule and that that low levels of overexpression of DmTNFv2 in transgenic flies leads to lethality.

Since the instant specification does not disclose a credible "real world" use for the claimed invention, it is incomplete and, therefore, does not meet the requirements of 35 U.S.C. §101 as being useful.

Claim Rejections - 35 USC § 112, first paragraph, maintained.

10. Claims 41-66 stand rejected under 35 USC 112, first paragraph is maintained for reasons set forth in Paper No: 11 and paragraph 8 above. Applicant's arguments filed on 8/06/03 in reference to claims 41-63 have been fully considered but they are not persuasive.

11. The rejection of claims 41,46, 48, 50, 51, 58 –60 and 64-66. under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained. Applicant's arguments filed on 8/06/03 in reference to claims

41-63 have been fully considered but they are not persuasive. Although, Applicant has removed the fragments thereof language from the claims, Applicants still contemplate isolating polynucleotides that hybridize under stringent conditions to nucleotides that encode various regions of SEQ ID NO: 6 and also polynucleotide sequences which are at least 80% identical to those isolated from claim 41 and have a TNF activity. It is unclear from the recitation what TNF activity is contemplated in the instant invention. In addition, it is also unclear what regions of the polypeptide are required to confer this activity. The claims as written, however, encompass various nucleotide sequences which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph because the written description is not commensurate in scope with the recitation of claims 41,46, 48, 50, 51, 58 –60 and 64-66. The specification does not provide written support for the genus encompassed by the instant claims.

12. The rejection of claims 41,46, 48, 50, 51, 58 –60 and 64-66 under 35 U.S.C. 112, first paragraph, as containing subject matter, which was not enabled is maintained. This enablement rejection is maintained. Applicant's arguments filed on 8/06/03 in reference to claims 41-63 have been fully considered but they are not persuasive. Although, Applicant has removed the fragments thereof language from the claims, Applicants still contemplate isolating polynucleotides that hybridize under stringent conditions to nucleotides that encode various regions of SEQ ID NO: 6 and also polynucleotide sequences which are at least 80% identical to those isolated from claim 41 and have a

TNF activity. It is unclear from the recitation what TNF activity is contemplated in the instant invention. In addition, it is also unclear what regions of the polypeptide are required to confer this activity. The specification only describes a single polypeptide and fails to teach or describe any other molecules that meet the structural limitations of the claims. The breadth of the claims is such that the claims encompass polypeptides from other species and related polypeptides that have yet to be described. There is a lack of guidance or teaching regarding structure and function of the polypeptide because there is only a single example of a polypeptide provided in the specification and because there is no guidance found in the prior art for this specific polypeptide.

The claims as written, however, encompass various nucleotide sequences which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph because the written description is not commensurate in scope with the recitation of claims 41,46, 48, 50, 51, 58 –60 and 64-66. The specification does not provide written support for the genus encompassed by the instant claims.

Claim Rejections - 35 USC § 112, first paragraph is withdrawn

13. The rejection of claim 41 under U.S.C. 112, first paragraph for reciting a "mature polypeptide" is also withdrawn because of Applicants arguments are deemed persuasive.

Claim Rejections - 35 USC § 112, second paragraph is withdrawn

14. The rejection of claims 41 and 54 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention is with drawn in light of Applicants arguments and amendments to the claims.

Claim Rejections - 35 USC § 102, maintained

15. The rejection of claims 41, 51, 58 and 62 under 35 U.S.C. 102(b) as being anticipated by Celniker et al (AC005974, 1998) is maintained. Applicant's arguments filed on 8/06/03 in reference to the original claims 41-63 have been fully considered but they are not persuasive. Applicant argues that the fragment described in Celinker et al does not encode for TNF domain and thus does not TNF activity. As indicated above in paragraphs 10 and 11 it is not clear what TNF activity is contemplated by the Applicants. Therefore, the disclosure of Celniker et al., anticipates claims 41, 51, 58 and 62.

16. New claim rejection necessitated by Applicants amendments.

Claim Rejections - 35 USC § 112

17. Claims 41, 58, 62, 63 and 66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

17a. Claims 41, 58, 62, 63 and 66 are rejected as vague and indefinite for reciting " TNF activity". It is unclear what TNF activity is contemplated by the Applicants.

18. Claims 62, 63 and 66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide of SEQ ID NO: 6 (amino acids 1 to 409 or amino acid 53-409), does not reasonably provide enablement for amino acid

sequences of SEQ ID NO: 6 (amino acids 1-315, 316-332 and 333-409). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is unclear which fragments are required to confer the "TNF activity". It is also not clear what TNF activity is contemplated. Claims 62, 63 and 66 are describing three mutually exclusive amino acid fragments yet the three claims assert that they have TNF activity, for example, amino acids 1-315, 316-332 and 333-409. Despite knowledge in the art for producing polypeptides, the specification fails to provide any guidance regarding the proteins produced by the contemplated amino acid fragments and yet retain the function is lacking. Furthermore, detailed information regarding the structural and functional requirements of the disclosed protein is lacking. Although it is accepted that the amino acid sequence of a polypeptide determines its structural and functional properties, predicting a protein's structure and function from mere sequence data remains an elusive task. Therefore, predicting which amino acid fragments, if any, would retain the "TNF activity" of the protein is well outside the realm of routine experimentation. Thus, an undue amount of experimentation would be required to generate the changes/modifications contemplated and yet retain the function of the proteins claimed.

Applicants have not taught how one of skill in the art would use the full scope of polypeptide sequences encompassed by the invention of claims 62, 63 and 66. The specification as filed does not sufficiently teach one of skill in the art how to make and/or

use the full scope of the claimed sequences. The amount of experimentation required to make and/or use the full scope of the claimed sequences would require trial and error experimentation to determine the functional sequences. Given the breadth of claims 62, 63 and 66 in light of the unpredictability of the art as determined by the lack of working examples and shown by the prior at of record, the level of skill of the artisan, and the lack of guidance provided in the instant specification, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

19. No claims are allowed.

20. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-0294 for regular communications and 703-308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JS
December 1, 2003

LORRAINE SPECTOR
PRIMARY EXAMINER